Behavior and Characteristics of Squamous Cell Carcinoma of the Perianal Region: A Pilot Study

Table of Contents

Glossary

AJCC: American Joint Committee on Cancer

SCC: Squamous Cell Carcinoma

CIS: Carcinoma in situ

BWH: Brigham and Women's Hospital

BWH-T: Brigham and Women's Hospital Tumor Staging System

BWFH: Brigham and Women's Faulkner Hospital

MGH: Massachusetts General Hospital

APR: Abdominoperineal resection

Introduction:[1]

Squamous Cell Carcinoma (SCC) is a malignant tumor of epidermal keratinocytes. It is an extremely common cancer, second in the United States only to basal cell carcinomas, and comprises approximately 20% of all non-melanoma skin cancers.[1] SCC exists on a spectrum of disease ranging from precursors such as dysplasia and carcinoma in-situ (CIS) to locally invasive disease and finally to metastatic disease. Because SCC is so common, its incidence is not explicitly tracked as other cancers are, and it is thus difficult to accurately estimate to proportion of cases falling into each of the above categories. However, previous studies have estimated that there are between 186,000-419,000 cases of invasive SCC in the US in 2012.[2] Furthermore, the incidence appears to be rising, which may be in part due to increased exposure to risk factors, better detection of SCC, and an aging population.[3]

SCC are sometimes classified with respect to domains such as morphology and behavior, histologic appearance, and body location. Though SCC were traditionally grouped as one entity, there has been increased recognition of the fact that differences in any of these domains may play an important role in defining the care of patients with these tumors. An example of how such differences may be relevant to the care of patients is of central importance in this study. For instance, sun exposure (particularly UV exposure, and primarily UVB) has long been implicated as the key risk factor for the development of cutaneous SCC's, though SCCs that develop in the perianal region seem to do so without much, if any, UV exposure and thus have escaped this dogma.[4] Instead, recent research suggests that these perianal SCC may have distinct etiologies and that their development is more closely related to a unique set of factors such as concurrent HPV infection, immunosuppression such as HIV infection, smoking status, or chronic inflammatory conditions affecting the perianal region.[5-7]

[1] Parts of this work were previously reported as part of the scholarly project proposal submitted to Scholars in Medicine Office (Halim K., Karia P., Schmults C. [2014] Scholarly Project Proposal.

Because the risk factors for perianal SCC described above are different than those of cutaneous SCC, questions have arisen about whether perianal SCC are best classified with other cutaneous SCC. Though perianal SCC are currently grouped with cutaneous cancers, the risk factor profile for perianal SCC is actually more similar to SCC of the anus. In addition to similar risk factors, the behavior of perianal SCC has been speculated to more closely mirror that of anal SCC. For instance, while cutaneous SCC have an excellent prognosis because they rarely metastasize, anal cancers may invade lymphatics and metastasize, leading to a worse prognosis.[8] This research begins to address whether perianal cancers behave more as cutaneous SCC or anal SCC.

Better characterizing the behavior of perianal SCC may improve care in several ways. Anal canal SCC, because of its worse prognosis, is predominantly handled by gastroenterologist/oncologist teams. Over the years, treatment paradigms in this field have shifted towards chemoradiation as opposed to previously preferred abdominoperineal resection.[9] This treatment modality is in stark contrast to cutaneous SCCs which can almost always be treated with resection and without the need for chemoradiation because they are inherently unlikely to metastasize.[10] Because of this uncertainty regarding the behavior of perianal SCC, staging, classification and ultimately the treatment of these tumors in patients is left to the judgment of the practitioner. By unifying and conclusively categorizing these tumors, we hope to open the door for additional research pursuits specifically targeted at improving the care of these patients.

Cancer staging is a crucial element in the care of the cancer patient for several reasons. Primarily, it is a determinant of what types of treatments a patient is eligible for. By dividing cancers into stages, it can be known for instance that in most cases a localized cancer may not benefit from additional total systemic chemotherapy, whereas a more advanced stage cancer has a different risk-benefit ratio that may warrant more aggressive diagnostics and therapies. Additionally,

staging systems have a prognostic component to them as well, meaning that patients with similar disease extents can be followed over time and predict, as a whole, how they will fare.

Despite the developing thinking that perianal SCCs may be more similar to anal SCC than to cutaneous SCC, this problem is not resolved simply by determining which group perianal SCC should belong to. For instance, if clinical practice were to start staging perianal SCC by the corresponding anal SCC staging guidelines instead of cutaneous staging guidelines, practitioners may find that the anal staging guidelines also do not accurately represent perianal SCC. We wondered therefore whether either staging system currently in place is adequately suited to stage perianal SCC. There is precedent for a unique staging system to be developed for SCC of a particular body region, which was done after it was recognized that the eyelid, with its own unique anatomical considerations, deserves its own staging system for SCC.[11,12] This therefore sets a precedent for treating SCCs which arise on different body regions differently, and to also develop unique staging system which better take into account the salient features of the tumors that arise in the perianal area.

The staging system most widely used for cutaneous SCC is the American Joint Committee on Cancer (AJCC) system. Also developed within the last few years is the Brigham and Women's Hospital Tumor (BWH-T) system which was found to outperform the AJCC guidelines for cutaneous SCC.[13] The performance of a staging system is judged by three parameters: whether it is distinctive (outcomes vary between groups), whether it is homogenous (outcomes are similar within a group), and whether it is monotonous (outcomes worsen with progressive stages).[13] The BWH-T guidelines were able to outperform in these parameters by modifying the criteria used to upstage a tumor based on histologic features such as lymphovascular invasion and perineural invasion. The BWH-T system was developed specifically with these features in mind because they are more predictive of aggressive tumors, such as those arising in perianal skin.

There is also a set of guidelines from the AJCC on staging practices for anal SCC. To the author's knowledge, these have not been investigated for their ability to stage perianal SCC accurately. Sufficient data was collected to stage the cohort of perianal tumors by AJCC anal guidelines, AJCC cutaneous guidelines, and the modified BWH-T guidelines. As previously discussed, perianal SCC, when staged by the current cutaneous SCC staging systems, do not behave as expected in terms of disease outcomes, often exhibiting more aggressive behavior than expected for a given stage. This has been taken into account in developing a staging system that is similar but not identical to the now validated BWH-T system and it may outperform any of the existing staging guidelines, because it specifically takes into account the features of perianal SCC.

Therefore, the ultimate goals of developing a modified BWH-T staging system were to stage perianal SCC independently of cutaneous or anal SCC with better accuracy than either set of guidelines can currently offer. We compared the key characteristics of an adequate staging system (distinctiveness, homogeneity, monotonousness).

An additional aim was to assess and describe the perianal SCC population in a systematized way at the Brigham and Women's Hospital and Massachusetts General Hospital, as well as to describe the outcomes of their SCC disease. By compiling this information regarding risk factors, recurrences, and outcomes, a wealth of knowledge about the course and extent of disease in this patient population will be created. By gathering data on HPV co-infection, immunosuppression status, and other key comorbid illnesses, risk factors will be identified, some of them potentially modifiable that could be touted as ways to lessen the prevalence of perianal disease in the future. Ultimately we hope that this study improves the care of patients with perianal SCC.

Methods

The BWH-T staging system was modified to better represent the unique considerations of perianal SCCs. Unlike the AJCC anal cancer staging guidelines or the AJCC non-eyelid carcinoma guidelines, a greater emphasis was placed on "high-risk factors" in this system (Table 1). In addition, the threshold for differentiation counting as a high-risk factor was changed to have both poor or moderate differentiation counting. Tumors of exactly 2cm were also included as a high risk factor, whereas the AJCC required tumors to be greater than 2cm.

Once the guidelines were established, the first phase of the project was to do a smaller pilot study based on literature reports of applicable SCCs. For this, the existing literature was reviewed for all reported cases of anogenital SCC with sufficient tumor information and outcome data to accurately stage using the AJCC and BWHT systems. Penile and vulvar SCC were excluded from this phase of the study because there were a relatively small number of cases in the literature that contained all of the necessary data in the publication to include in this study.

During the first phase of the study, approximately 400 abstracts were reviewed, and 130 papers were read to find 56 cases that were of use in the study. In these 56 cases, demographic data, staging data, and outcome data was recorded for all of them. However, because these 56 cases were divided amongst the three different locations (penile, vulvar, and perianal), it was ultimately decided that it would not be possible to develop a staging system from such small numbers of patients in each.

Therefore this investigation is a retrospective pilot study of patients at a single institution of perianal SCC. Due to the relative scarcity of these tumors, a prospective study would have taken many years to perform. Patient selection was pursued using an RPDR billing code search for "malignant anal neoplasm". The search was limited to the years 2000 through 2009, in order to allow for at least 5 years of possible follow-up and to also ensure adequate medical record

documentation. Three hundred eighty-nine patients were identified from the Brigham and Women's Hospital meeting these criteria and an additional 390 from the Massachusetts General Hospital. After excluding duplicates, there were 566 unique patients.

With 566 total patients in the initial database, it was estimated approximately 20% would be included in the final analysis. However upon final analysis, this figure is closer to 10%, yielding 52 total patients for inclusion in the study. These 52 medical records were reviewed with the aim of gathering demographic information, pathological information necessary for staging, and all relevant outcome data.

The most subjective component of the chart review was defining precisely each patient's anatomy with respect to the area in which the tumor arose. SCC may develop in the neighboring anal canal or anal mucosa, in which case it is a different class of tumor and was excluded from this study (Figure 2). Tumors that arose primarily on the perianal skin distal to the anal verge were included. This distinction was made by reviewing documentation from examining physicians including oncologists, dermatologists, surgeons, and gastroenterologists. Pathology reports were also scrutinized to determine the nature of the surrounding tissue (for instance, mucosa vs hair-bearing skin). Radiology reports were sometimes utilized as well for detailed information regarding anatomy.

Patients were also excluded if their tumor was found to be a recurrent one, if they did not have a cutaneous perianal SCC as determined above, or if there was inadequate documentation in the medical record to gather comorbidities or tumor information.

The data was first analyzed qualitatively to compare cohort characteristics with respect to local recurrences, nodal recurrence, distant recurrence, disease specific death and overall death between the two staging systems. Patients with bad outcomes of all types were all scrutinized to identify salient features of their history

and tumor characteristics. Given the completely novel nature of this study in the SCC literature, a preliminary study that identifies predictive features of morbid perianal SCC tumors and demonstrates qualitatively the performance of the BWH-T system contributes greatly to the SCC body of knowledge. We also performed statistical analysis to determine what comorbidities or demographic features might independently predict poor outcomes. Finally, we performed a multivariate analysis to identify which factors were predictive of poor outcomes.

Data analysis was performed using STATA and was performed at the Brigham and Women's Faulkner Hospital. The work was based out of the Brigham and Women's Faulkner Hospital. All data has been stored securely. There are no other parts of this project being conducted by other researchers or groups.

Results

After identifying the initial 566 patients, patient charts were reviewed to determine which of the initial patients met inclusion criteria. Of the 779 results in the RPDR search, 213 were found to be duplicate patients seeking care at both hospitals. Of the remaining 566, twenty-four were excluded due to their diagnosis occurring outside the specified study date (2000-2009); 131 were excluded because their cancer was not SCC; 220 were excluded because their SCC was deemed to occur at a point proximal to the anal verge; 25 were excluded because their tumors were recurrent; 51 were excluded because their medical records had inadequate data to completely characterize their tumors and outcomes (for instance if only their pathology slides were sent to our facility for consultation), as well as "other" reasons; 63 were excluded because there was no definite area of invasion in the biopsy specimen (Figure 1).

This process left 52 patients to analyze for this study. Baseline cohort demographics are presented in Table 2. The patient cohort was predominantly white (90.4%) and female (57.7%). The median age at the time of the patient's diagnostic biopsy was 55. Forty percent of patients were single, with an equivalent percentage married and the remainder were either divorced or widowed. The average time of follow-up for patients from date of biopsy was a median of 5.1y, with a range of 0-13.8y. A large percentage (38.5%) of patients were immunosuppressed, with the most common reasons including documented HIV infection (n=13) and organ transplant (n=3). A majority had a documented smoking history (69.2%) and many also were documented as being HPV positive at some point either before or after their perianal SCC diagnosis (42.3%). Additionally upwards of 30% had some form of perianal disease which was defined as inflammatory bowel disease (both Crohn's and Ulcerative Colitis), hemorrhoids, fissures, and genital condyloma, with in excess of half of these comprised by condyloma. Twenty-two patients (42%) had been diagnosed with another cancer before or during their SCC follow-up.

With regards to staging, a consensus stage was reached for 45 of the 52 tumors using the AJCC cutaneous and anal staging system and 46 of the 52 tumors using the BWH-T staging system. The majority of the tumors were stage T1 in all groups (n=27, AJCC cutaneous; n=31, AJCC Anal; n=22, BWH-T). However, while the remainder of the stageable tumors were classified as T2 in the AJCC system (n=18 cutaneous; n=13 anal), the remaining tumors in the BWH-T system were split between the groups T2a (n=15) and T2b (n=9).

Tumors were an average of 1.84cm in diameter, though ranged from 0.2cm tumors with small foci of invasive SCC to a large 9.5cm tumor. Tumor differentiation was divided between well, moderate and poor, as well as overlapping between two divisions, with many tumors being reported as at least partially moderately differentiated (n=23). However, 15 tumors were not assigned any degree of differentiation in the pathology reports. Two tumors exhibited some degree of lymphovascular invasion under pathologic examination, while none of the pathology reports commented on the presence of perineural invasion.

Patients were treated with either resection or chemoradiation, and in some cases both. Resection was the only primary treatment modality in 44% of patients (n=23). In comparison, 31% (n=16) of patients were treated exclusively with chemoradiation. The remainder received some combination thereof, with at least part of the tumor being debrided or resected along with chemoradiation treatment (n=12).

Bad outcomes were classified as either local recurrences, nodal metastases, distant recurrence (metastasis) and death from SCC. There were 6 local recurrences, 2 nodal recurrences, 4 distant metastases and 3 deaths from SCC. The outcomes were both sporadic and progressive; some patients who died from their SCC had local, nodal, and distant recurrences prior to death, while one patient had an isolated distant metastasis without death or other recurrence.

Table 3 demonstrates in detail features of patients with bad outcomes. There were 10 total patients experiencing at least a local recurrence. Patients with poor outcomes appeared to differ in several ways from patients without a poor outcome. By qualitative analysis, patients with bad outcomes are in general older, frequently immunosuppressed, have very high rates of HPV, other STI, and viral hepatitis co-infection. There is also a significant minority who have chronic perianal disease or inflammation and have been diagnosed with other cancers.

Of the 9 patients who had enough data documented in their charts to be staged, 5 were assigned a T2 stage by AJCC anal guidelines and 4 were assigned T1 stage. There was one T3 AJCC anal tumor in the 52 patient cohort, however this patient did not have a poor outcome. AJCC cutaneous guidelines more frequently upstaged tumors to T2 than the AJCC anal stage guidelines (7 out of 9 were T2 cutaneous stage). However, the BWH-T seemed to most readily upstage this cohort of patient tumors, staging only one as a T1 type tumor. Two of the remaining 8 were classified as T2a, while 6 of the 9 tumors were designated as T2b tumors.

When we performed a univariate analysis, several factors appeared to be independently predictive of a poor outcome. Age >55 (HR 6.0, $p<0.05$), tumor diameter ≥3.0cm (HR 5.5, $p<0.05$), and tumor invasion into subcutaneous tissue or beyond (HR 4.9, $p<0.05$) were all independently predictive of a poor outcome. When we performed a multivariate analysis, age >55 (HR 13.8, $p<0.05$), tumor diameter ≥ 3.0cm (HR 6.1, $p<0.05$) and HPV infection (HR 4.7, $p<0.05$) were all predictive of a poor outcome.

Discussion

This challenging study endeavored to, for the first time, evaluate the appropriateness of different staging systems currently used for staging perianal SCC. The ultimate aim of this study was to further the treatment of patients with perianal SCC by better defining their tumors and need for various cancer therapies. Though there were many challenges, progress was made in achieving some of the initial goals.

Our preliminary analysis revealed that for the cohort of patients who had recurrent perianal SCC in our study, the Anal AJCC guidelines least frequently predict a bad outcome by assigning those tumors a high stage, the Cutaneous AJCC guidelines are intermediate in predicting a bad outcome, and the BWH-T guidelines most frequently assign a high stage to tumors with eventual poor outcomes. This may be due to the restrictive nature of the AJCC guidelines, particularly with respect to assigning a high T3 or T4 stage (only one T3 tumor in our 52 patient cohort). This means that all poor outcomes occurred in low AJCC tumor stages, and the T3 tumor did not have a poor outcome. Conversely, 60% of all the poor outcomes occurred in BWH-T high stage (T2b or T3) tumors. This also means however that 40% of the high stage tumors according to the BWH-T system did not have a poor outcome.

Though this is encouraging and serves to guide additional investigation, several questions remain unanswered. For instance, it may be that BWH-T too readily assigns a high stage to tumors, and therefore predicts bad outcomes even for tumors that prove to benign. However, our preliminary data suggest this is not a major factor; BWH-T staged 9 total tumors of 52 as T2b, of which a majority (6), appeared in the final bad outcome cohort. Further research will be required to conclusively determine whether this is a favorable tradeoff.

Because of the comprehensive nature of the data collection in this study, it was possible to analyze the data for features predictive of poor outcomes. The data demonstrate that tumor size, old age, and HPV infection are predictive of poor

outcomes in perianal SCC. In addition, patients with poor SCC outcomes have high rates of co-morbid conditions including immunosuppressed statuses, other cancers, inflammatory conditions of the perianal region, smoking histories, and documented HPV positive status. These preliminary findings put in place a framework for future studies seeking to develop a predictive model on the basis of the presence of these factors. A larger study will be needed to additionally validate the individual predictive elements of the staging systems currently in place, with the possible exception of tumor diameter which was shown to be predictive in this study.

The high number of bad outcomes (recurrences and death) that occurred in our population was surprising. Approximately 20% of patients experienced a poor outcome, a proportion far greater than what would be expected for cutaneous SCC, again lending credence to the argument that perianal SCC do not behave quite like cutaneous SCC. However, caution must be taken in making this claim since the selection and classification of these tumors was subject to the biases of a retrospective chart review, and may represent tumors that were not truly cutaneous tumors.

Also of note in the patient population was the primary treatment modality employed. Though abdominoperineal resection (APR) was once the favored treatment modality for anal cancers involving the anal sphincter muscles, the desire to spare this vital anatomic structure has led to the finding that chemoradiation is both safe and effective for patients with anal canal carcinoma.[14] Local resection is still employed for tumors not involving the sphincter, and APR is still used as a salvage treatment. In our cohort, a minority actually received chemoradiation alone, suggesting that smaller, less invasive tumors were resected without chemoradiation, in a manner similar to the treatment of cutaneous SCC. However, because this paradigm shift towards chemoradiation occurred in the late 1990s and into the early 2000's, we cannot be certain whether patients in the earlier part of our cohort were being treated with APR due to the delayed uptake of new evidence-based practice guidelines.

Among the aforementioned challenges, perhaps foremost are the difficulties posed by the complex anatomy of the perianal area (Figure 2) and determining whether a tumor arose primarily from perianal, hairbearing skin distal to the anal verge or whether it was a tumor of the anal mucosa proximal to the anal verge. There is also often confusion regarding terminology and the distinction between the anal verge and the anal margin: according to the World Health Organization, the anal verge is the most proximal part of the anal margin where the squamous epithelium of the anal canal meets the skin and then extends 5cm outwards.[15] Tumors of the anal margin were included in the study, those involving the anal epithelium and proximal were not.

Compounding this anatomical confusion is the fact that the anal verge is more of an embryonic boundary, and is not made readily on clinical grounds as compared with boundaries such as the dentate line. As a result surgeons use more appreciable boundaries when operating in order to define the anal canal, such as the anorectal ring. Finally, the focus of invasive SCC rarely arises in otherwise healthy tissue. Many times the site would be listed as “anal polyp”, “anal condyloma”, or “arising within an anal fissure”. All of these outgrowths are not inherent to any anatomical region, and leave much uncertainty as to their origin and how the tumor should be ultimately classified. We feel strongly that a consensus should be reached regarding terminology and clear definitions be proposed that are not merely anatomically accurate but also are practically useful in clinical medical practice.

It is perhaps not surprising then that after looking at several different documents in the medical record, rarely was there a consensus regarding the origin of the tumor. The same tumor could be described differently by each the dermatologist, surgeon, or gastroenterologist, and all may have a different opinion than the oncologist or pathologist. Opinions regarding the origin of the tumor also change as additional data come in, as is often the case following resection of a perianal tumor, which after inspection of the pathologic specimen removed may be a tumor which is clearly

a tumor arising from the anal canal. Other times, the analysis is complicated by areas of invasive SCC arising in a bed of SCCIS, leading the practitioner to wonder if there is invasive SCC elsewhere in the bed of SCCIS that simply was not biopsied or resected.

Judgments regarding treatment in these ambiguous cases may be influenced by the frequency and availability of biopsy. Even if the invasive SCC biopsy is taken from perianal skin, the existence of SCCIS extending into the anal canal does not preclude the fact that the tumor may in fact have a mucosal component. In these scenarios, it is perhaps reasonable for the clinician to adopt a defensive stance, and to treat any unresolvable ambiguity regarding a tumor as evidence of its mucosal origin and proceed to chemoradiation therapy as opposed to simple excision. While this practice undoubtedly has the patient's best-interests in mind (with regards to trying to achieve cure and minimize the odds of recurrence or spread in the future) it is uncertain based on the data currently available in the literature whether this practice achieves its end. What it does clearly do however is expose patients to the additional risks of chemoradiation, while perhaps sparing them the risks/harms of resection. The cost/benefit ratio of this substitution is also unknown, however we suggest that this serve as a major area of future investigation.

Perhaps the most eloquent statement of what we know and what remains ambiguous is found written in a patient note, quoted below:

"*Although there is literature supporting local excision for perianal lesions that involve the skin without involving the anal canal, for true anal canal lesions local excision is associated with a higher recurrence rate than chemo-radiation, and for this reason chemotherapy and radiation is the standard treatment recommendation. Although one of the excisions did describe hair follicles in the specimen, the surgeon describes the primary lesion as a polyp within the rectum, and rectal mucosa was also visible in the excision. I have had the opportunity to review the pathology specimens with Dr. [redacted], who confirmed that there was invasive squamous cell*

carcinoma arising in a background of anal carcinoma in situ, and that the lesion was not based in the perianal skin."

Therefore, this speculative though collaborative approach may be imperfect. Perhaps then it is most prudent to do what physicians do in other situations that are also ambiguous, and this is to leave it up to patients to decide the best course of action, after informing them what we know and what the known risk/benefits of each strategy are. Furthermore, a greater emphasis should be placed on resolving this ambiguity through improved communication between providers, for instance by forming committees that would decide how to treat ambiguous tumors.

Communication with patients and between patients can only be viewed as a temporizing measure, until further research can be performed in patients whose tumors continue to elude standard classification even after the above measures have been undertaken. This research will likely need to take the form of prospective randomized study that splits patients with ambiguous tumors into a chemoradiation arm and a surgical resection arm. While the primary outcome of such a study should be mortality, an important secondary outcome should be some measure of adverse effects and quality of life of treatment, since one treatment may be more morbid than the other and thus preferable to certain patients in certain scenarios.

An additional major challenge encountered in this study is the often incomplete documentation in both the clinical history and pathology reports. In order to accurately stage a tumor using the AJCC system, the maximal diameter and depth in centimeters of the tumor must be known, as well as the degree of differentiation, depth with regards to level of tissue invaded, presence of perineural invasion, and site of the tumor. For the BWH-T system, it is also important know whether there is lymphovascular invasion. Pathology reports often simply reported "SCC, invasive" as the diagnosis without additional information. These reports were assumed to be

complete, and therefore if a parameter was not specifically commented on it was assumed to be negative or absent.

Records of tumor size varied greatly between practitioners, and while pathology reports consistently defined the size of the specimen, the specimen was most likely not representative of the tumor (the specimen was either a biopsied portion of the tumor, or if removed en masse, contained non-tumor tissue as well). Therefore we suggest that when reporting histological aspects of a tumor and also in recording its size, there is a clear need for standardization of the reporting format by practitioners. Doing so will ensure appropriate staging for clinical purposes, but also allow for more precise future research.

Limitations to this study are the fact that this is a single institution study performed at a tertiary care hospital that was highly representative of elderly white patients, though perhaps less so of other groups and in other geographic regions. Therefore the generalizability of our results remains left to be determined. It was also a retrospective study in which the results were subject to bias, though steps were taken to minimize this effect whenever possible. We also have a relatively small cohort of patients, owing to the rarity of the disease in question. There were a small number of bad outcomes for patients which likely means that our population was underpowered to truly measure the full benefit of the BWH-T guidelines.

Further limitations include the limited expertise of some researchers in the medical, surgical, and oncologic management of perianal SCC. This is particularly important to this study because a thorough and accurate evaluation of candidate patients is necessary to establish a valid patient cohort. There are also only a limited number of practitioners involved in the care of these patients and practice patterns of the practitioners may not be representative of the population as a whole.

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This work was performed under the supervision of Dr. Chrysalyne Schmults, a Mohs surgeon and Assistant Professor at Harvard Medical School. She is also affiliated with the Dana-Farber Cancer Institute and has been on the faculty at Harvard since 2003. Dr. Schmults is an expert in the surgical management of challenging skin cancers; included amongst those are perianal SCCs. She herself has operated and treated many of the patients in our database, and is very knowledgeable on the subject. She developed the initial BWH-T staging system that has already been formally validated for cutaneous SCCs.

Pritesh Karia, MPH was also of vital importance to the completion of this study. Mr. Karia performed the RPDR search, assisted with study design, data scrutiny and analysis, the creation of tables and figures for the study and helped to frame the role of this study in the SCC literature.

Kareem Halim performed the initial literature search and review of literature cases. He helped with the design of the study and also performed the subsequent data gathering on the 566 patient cohort. He wrote this manuscript and performed part of the data analysis.

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Table 1. Summary of the American Joint Committee on Cancer Anal and Cutaneous Squamous Cell Carcinoma 7th Edition Staging Guidelines and the Brigham and Women's Hospital Tumor Staging System for Cutaneous Squamous Cell Carcinoma

AJCC Anus	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (i.e., Bowen disease, high-grade squamous intraepithelial lesion, and anal intraepithelial neoplasia II–III)
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but ≤5 cm in greatest dimension
T3	Tumor >5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, and bladder
AJCC Cutaneous Squamous Cell Carcinoma	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor ≤2 cm in greatest dimension with <2 high-risk features
T2	Tumor >2 cm in greatest dimension or tumor any size with ≥2 high-risk features*
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base
BWH Cutaneous Squamous Cell Carcinoma	
T1	0 high-risk factors†
T2a	1 high-risk factor
T2b	2-3 high-risk factors
T3	4 high-risk factors or bone invasion

Abbreviations: AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; *AJCC high-risk factors include >2 mm thickness, Clark level ≥IV, primary site ear, primary site non-hair-bearing lip, and poorly differentiated histology; †BWH high-risk factors include tumor diameter ≥2 cm, poorly differentiated histology, perineural invasion ≥0.1 mm, or tumor invasion beyond fat (excluding bone invasion which automatically upgrades tumor to BWH stage T3).

Table 2. Baseline Cohort Characteristics

Patient Characteristics	**No. of Patients (n=52)**
Age, mean (standard deviation)	55 (12.7)
Sex, n (%)	
Female	30 (57.7)
Male	22 (42.3)
Race, n (%)	
White non-Hispanic	47 (90.4)
African American	3 (5.8)
Hispanic or Latino	2 (3.8)
Marital status, n (%)	
Single	21 (40.4)
Married	22 (42.3)
Divorced	5 (9.6)
Widowed	4 (7.7)
Smoking, n (%)	
No	16 (30.8)
Yes	36 (69.2)
Human papillomavirus infection, n (%)	
No	30 (57.7)
Yes	22 (42.3)
History of hepatitis, n (%)	
No	44 (84.7)
Yes	8 (15.3)

Table 2. Baseline Cohort Characteristics (Continued)

Patient Characteristics	**No. of Patients (n=52)**
History of sexually transmitted infection, n (%)	
No	38 (73.1)
Yes**	14 (26.9)
Human immunodeficiency virus	12 (85.7)
Herpes simplex virus	2 (14.3)
Syphilis	2 (14.3)
Gonorrhea	1 (7.1)
Chlamydia	1 (7.1)
Immunosuppressed, n (%)	
No	32 (61.5)
Yes	20 (38.5)
Human immunodeficiency virus	12 (57.1)
Organ transplant	3 (14.3)
Other*	5 (28.6)
History of perianal disease, n (%)	
No	36 (69.2)
Yes**	16 (30.8)
Hemorrhoids	8 (50.0)
Condyloma	2 (12.5)
Fissures	2 (12.5)
Inflammatory bowel disease	3 (18.8)
Lichen simplex	1 (6.3)
Lichen sclerosus	1 (6.3)
Perirectal fistula	1 (6.3)

Table 2. Baseline Cohort Characteristics (Continued)

Patient Characteristics	**No. of Patients (n=52)**
Other cancer diagnosis, n (%)	
No	30 (57.7)
Yes	22 (42.3)
Kaposi's Sarcoma	4 (18.2)
Vulvar cancer	4 (18.2)
Non-melanoma skin cancer	4 (18.2)
Anal canal cancer	2 (9.1)
Prostate cancer	2 (9.1)
Breast cancer	1 (4.6)
Endometrial sarcoma	1 (4.6)
Hodgkin's lymphoma	1 (4.6)
Lung cancer	1 (4.6)
Oropharyngeal cancer	1 (4.6)
Renal cancer	1 (4.6)
Tumor Characteristics	**No. of Tumors (n=52)**
Tumor diameter (cm), mean (standard deviation)	1.8 (1.6)
Depth of tumor invasion, n (%)	
Dermis	15 (28.9)
Subcutaneous fat	3 (5.8)
Submucosa	1 (1.9)
Muscle	4 (7.7)
Unknown/not recorded	29 (55.7)

Table 2. Baseline Cohort Characteristics (Continued)

Tumor Characteristics	**No. of Tumors (n=52)**
Tumor differentiation, n (%)	
Well	13 (25.0)
Moderate	16 (30.8)
Poor	9 (17.3)
Unknown/not recorded	14 (26.9)
Perineural invasion, n (%)	
No	51 (98.1)
Yes	1 (1.9)
Lymphovascular invasion, n (%)	
No	50 (96.2)
Yes	2 (3.8)
Primary treatment, n (%)	
Resection	23 (44.2)
Radiation and chemotherapy	16 (30.8)
Resection, radiation and chemotherapy	12 (23.1)
Resection and radiation	1 (1.9)
Imaging studies, n (%)	
No	13 (25.0)
Yes	39 (75.0)
CT	32 (82.1)
PET	5 (12.8)
MRI, CT and PET	1 (2.6)
MRI and PET	1 (2.6)

Table 2. Baseline Cohort Characteristics (Continued)

Tumor Characteristics	**No. of Tumors (n=52)**
AJCC anal cancer tumor (T) stage, n (%)	
T1	31 (59.6)
T2	13 (25.0)
T3	1 (1.9)
Indeterminate	7 (13.5)
AJCC cutaneous squamous cell carcinoma tumor (T) stage, n (%)	
T1	27 (51.9)
T2	18 (34.6)
Indeterminate	7 (13.5)
BWH cutaneous squamous cell carcinoma tumor (T) stage, n (%)	
T1	22 (42.3)
T2a	14 (26.9)
T2b	10 (19.2)
Indeterminate	6 (11.6)

*Other reasons for immunosuppression include: chronic obstructive pulmonary disease (1), chronic renal failure (1), and psoriatic arthritis (1); **Percentages may not add to 100 because some patients had more than one type of condition.

Table 3. Characteristics of Patients that had a Poor Outcome during the Study Period

Patient	Age	Sex	Immunosuppression	HPV	STI	Perianal Disease	Primary Treatment	Outcome(s)	Tumor (T) Stage		
									AJCC Anal	AJCC Cutaneous	BWH Cutane
1	74	M	Y: chronic renal failure	Y	N	N	Resection	LR, DM, DD	T1	T2	T2b
2	83	F	N	N	N	N	Resection	LR	T2	T2	T2a
3	55	F	N	N	N	Y: hemorrhoids	Resection, Radiation	LR	--	--	--
4	56	M	Y: HIV	Y	Y: HSV, HIV	N	Radiation, Chemotherapy	LR	T1	T1	T2a
5	86	F	N	N	N	Y: hemorrhoids, lichen simplex	Resection	NM	T1	T2	T2b
6	62	M	N	Y	N	N	Resection	NM	T2	T2	T2b
7	40	F	N	Y	N	N	Resection, Radiation, Chemotherapy	DM, DD	T2	T2	T2b
8	82	F	N	N	Y: Syphilis	N	Radiation, Chemotherapy	DM	T2	T2	T2b
9	49	F	Y: psoriatic arthritis	Y	N	Y: hemorrhoids	Radiation, Chemotherapy	LR, DM, DD	T2	T2	T2b
10	64	M	N	N	N	N	Resection, Chemotherapy	LR	T1	T1	T1

Abbreviations: HPV, human pappiloma virus; STI, sexually transmitted infection; AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; HIV, human immunodeficiency virus, HSV, herpes simplex

Table 4. Results of Univariate Analysis of Risk Factors Associated with Poor Outcomes*

Variable	HR (95% CI)	*p* value
Age, years		
<55	1.0	
≥55	6.0 (1.3-28.4)	0.024
Sex		
Female	1.0	
Male	0.8 (0.2-2.9)	0.740
Smoking		
No	1.0	
Yes	0.3 (0.1-1.2)	0.097
HPV infection		
No	1.0	
Yes	1.4 (0.9-4.9)	0.210
Immunosuppressed		
No	1.0	
Yes	0.7 (0.2-2.7)	0.591
History of perianal disease		
No	1.0	
Yes	1.3 (0.3-5.1)	0.738
History of other cancer		
No	1.0	
Yes	0.7 (0.2-2.6)	0.637
Tumor diameter, cm		
≤2.0	1.0	

>2.0 -<3.0	1.1 (0.1-6.1)	0.884
≥3.0	5.4 (1.4-20.7)	0.013

Table 4. Results of Univariate Analysis of Risk Factors Associated with Poor Outcomes*

Variable	**HR (95% CI)**	***p* value**
Tumor depth		
Dermis	1.0	
Subcutaneous fat and beyond	4.9 (1.3-18.6)	0.018
Histologic differentiation		
Well	1.0	
Moderate	1.7 (0.3-8.5)	0.514
Poor	3.4 (0.7-15.3)	0.118
Perineural or lymphovascular invasion		
No	1.0	
Yes	2.5 (0.3-19.9)	0.389
Primary treatment		
Resection	1.0	
Radiation + chemotherapy	1.6 (0.4-6.2)	0.535
Resection + radiation + chemotherapy	0.5 (0.1-4.8)	0.571

*Poor outcomes include local recurrence, nodal metastasis, distant metastasis and death from disease; Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 5. Results of Multivariate Analysis of Risk Factors Associated with Poor Outcomes*

Variable	HR (95% CI)	*p* value
Age, years		
<55	1.0	
≥55	13.8 (2.4-31.0)	0.004
HPV infection		
No	1.0	
Yes	4.7 (1.1-20.6)	0.043
Tumor diameter, cm		
<3.0	1.0	
≥3.0	6.1 (1.5-24.3)	0.011

*Poor outcomes include local recurrence, nodal metastasis, distant metastasis and death from disease; Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 6. Poor Outcomes by the American Joint Committee on Cancer and Brigham and Women's Hospital Tumor Staging Systems[*]

Tumor (T) Staging System	**Risk of Poor Outcomes**	***p* value**
AJCC anus, n (%)		
T1/T2 (44)	20.5%	
T3 (1)	0.0%	--
AJCC cutaneous, n (%)[†]		
T1 (31)	12.9%	
T2 (14)	35.7%	0.111
BWH cutaneous, n (%)		
T1/T2a (36)	8.3%	
T2b/T3 (10)	60.0%	0.001

[*]Poor outcomes include local recurrence, nodal metastasis, distant metastasis and death from disease; [†]A comparison between low T stage (T1/T2) and high T stage (T3/T4) could not be made because no tumors were classified as high T stage.

Figure 2: Anatomy of Perianal Skin and Anal Canal

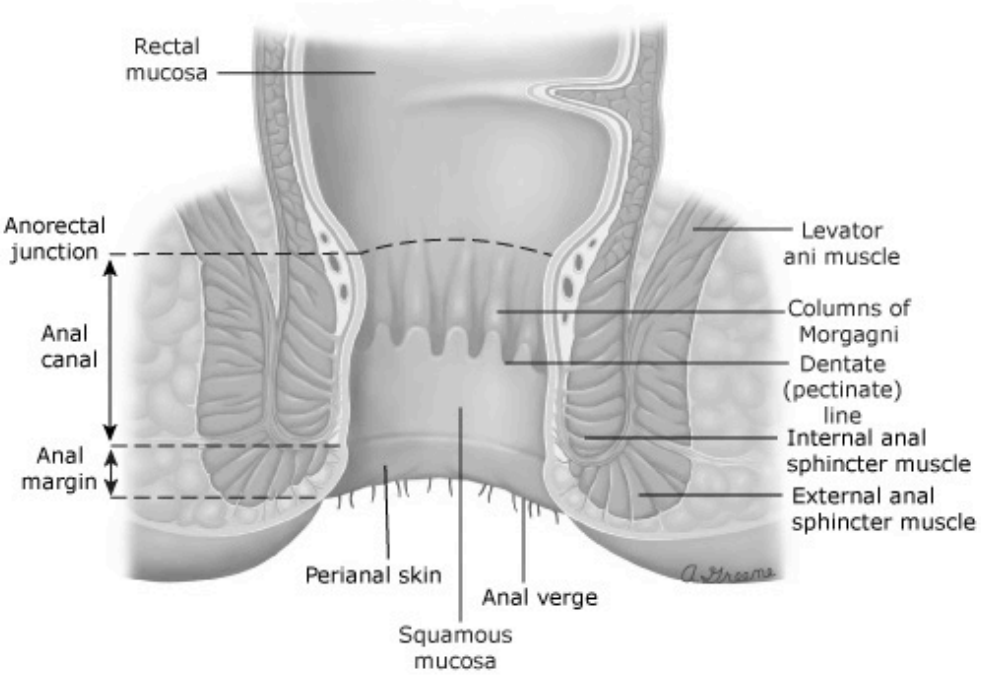

Figure 1: Reason For Exclusion and Final Cohort